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Reply to Eisen and McBryde

To the Editor—Eisen and McBryde [1] support the conclusion of our experimental study on antiplatelet prophylaxis of experimental infective endocarditis (IE) and the need to further investigate new drugs of the anti-GPIIb/IIIa receptor class (eg, abciximab) that could be given orally. Their argument is based on both the greater ability of abciximab than more classic aspirin-plus-ticlopidine regimen to prevent experimental IE caused by both streptococci and staphylococci, and on their meta-analysis showing that classical antiplatelet therapy given in established IE provided a benefit in terms of embolus prevention, which was counterbalanced by a risk of increased overall mortality. Thus, there is a proof of concept for a benefit of antiplatelet regimens in both IE prevention and therapy, but improved drugs and drug formulations must be sought.

We support the argument of Eisen and McBryde that further development on anti-GPIIb/IIIa drugs could represent an improvement for IE prevention in selected at-risk patients. However, we would not entirely discard a potential benefit from more classical antiplatelet regimens, as they did show a significant protective effect against experimental IE caused by both *Streptococcus gordonii* and *Staphylococcus aureus* experimental IE, although abciximab was more effective.

Eisen and McBryde's arguments are based on the relatively limited (although not null) efficacy of classical antiplatelet regimens (mainly aspirin) to prevent embolism in established IE. They also emphasize that antiaggregant therapy should be given before the onset of IE rather than after IE establishment. Indeed, early antiaggregant therapy may decrease the size of nascent vegetations and impede their further enlargement, whereas late antiaggregant therapy might favor vegetation dislodgment and bleeding in embolized areas [2].

The fact that antiaggregant given before IE is not a risk factor for increased embolism in case of later IE development is critical, as it does not prohibit antiaggregants as a prophylactic measure in at-risk patients, at least with classical drugs. The question, however, is whether or not chronic use of aspirin or other antiplatelet drugs might protect patients from IE development. We sought to determine whether existing human data could provide some clues to answer this question. Unfortunately, neither the Framingham Heart Study cohort nor the International Collaboration on Endocarditis database could provide definitive information on this specific issue. Therefore, we are currently planning a prospective observational study in patients with bioprosthetic heart valves receiving or not receiving thrombosis prophylaxis with antiplatelet drugs.

We also would like to emphasize the protective effect of the new-generation thrombin inhibitor dabigatran against *S. aureus* experimental IE. Control acenocoumarol did not protect against either streptococcal or staphylococcal experimental IE, whereas dabigatran specifically protected against *S. aureus* IE. This is likely associated with the observation that dabigatran inhibits not only thrombin, but also the *S. aureus* coagulase, which can bypass thrombin and polymerize fibrinogen into fibrin, even in acenocoumarol- or citrate-anticoagulated blood. The dual anticoagulant and anti–*S. aureus* activity of dabigatran would be ideal in patients with prosthetic valves, in whom *S. aureus* IE is lethal in close to 50% of cases [3, 4]. Unfortunately, dabigatran did not do well in such patients [5, 6]. While further pharmacologic development is required before dabigatran can be used in prosthetic valves, it opens yet another strategy for *S. aureus* IE prevention.

We agree with Eisen and McBryde that more developments are needed regarding the prevention and treatment of IE. Regarding prevention, we have abandoned antibiotic prophylaxis overkill, which was based on intuitive rather than evidence-based medicine [7, 8]. Yet, IE is a persistent Damocles sword in at-risk patients, as it can happen at any time during their life. Simple alternatives are needed for these patients, and chronic use of antiplatelet drugs could be one of them. Regarding therapy, 2–6 week courses of parenteral antibiotics are still the standard.

We think that numerous improvements are possible, including adjunctive therapy that could interfere with vegetation development, promote its resolution, and help bacterial clearance. Indeed, while further improvements in antiaggregant drugs seem a promising approach, other innovative options must also be considered, such as decreasing embolic events in patients suffering IE and chronically treated with statins [9], where pleomorphic activity might reveal as yet unexpected benefits. New imaginative strategies are welcome to solve the IE problem.

Note

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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